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Biliary dyssynergia : with an anatomical and physiological background

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B I L I A R Y D Y S S Y N E R G I A

With an Anatomical and Physiological Background

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Biliary Dyssynergia

Certain functional disorders of the gut tract, its sphincters and its appendages have been recognized and treated as clinical entities for many years. Yet, in spite of the facts that 400 years ago it was observed that there is an impediment to the flow of bile into the duodenum, and over 50 years ago circular muscle fibres at the distal end of the common bile duct were described and it was postulated that a dysfunction of this sphincter muscle might explain certain morbid dysfunctions of the biliary tract, clinicians and laboratory workers were slow to accept the fact that a functional disorder of this sphincter muscle might exist. And one is astonished to learn by perusal of the literature how indefinite is our knowledge of the physiology of the biliary tract at the present time. Experimental work and clinical observations are not meagre but they are conflicting to a remarkable degree.

The technical difficulties in all the experimental work of controlling extraneous factors are matched only by the difficulty in properly evaluating the results when they are obtained. Many authorities have been guilty of misconceptions merely because they failed to observe and recognize simple physical laws. Every theory and experimental fact advanced is attacked and discredited as soon as it is made known. Only now is a working foundation being slowly evolved from a confusion of contradictory ideas. Few indeed are the statements that can truly be made as facts.

The conception of functional disorders of the biliary tract has been gradually gaining support until now the literature on the subject has assumed moderate proportions and there is no doubt that it will receive permanent recognition as an entity.

With the above in mind a discussion of biliary dyskinesia or biliary dyssynergia will be presented on the basis of anatomic and physiologic facts insofar as these may be determined at the present time.

ANATOMY

The excretory apparatus of the liver is composed of four parts 1) the hepatic duct, 2) the gallbladder, 3) the cystic duct and 4) the common bile duct.

The hepatic duct is formed by the junction of two main trunks, one from the right lobe and the other from the left lobe of the liver.

The gallbladder is a musculo-membranous sac, lodged in a fossa on the under surface of the right lobe of the liver. It is about four times as long as it is wide and has a volume of 30 to 35 c.c. It is divisible into a fundus, a corpus, an infundibulum and a collum. The upper surface of the gallbladder is intimately attached to the under surface of the right lobe of the liver by a broad surface. The infundibulum of the gallbladder normally joins the collum of the gallbladder at an acute angle. There is a well marked constriction at the junction of the collum with the cystic duct. The mucous coat of the gallbladder is elevated into minute rugae. Opposite the collum the mucous membrane is projected inward

in the form of oblique ridges or folds, forming a sort of spiral valve (of Heister) continuous with similar oblique ridges in the cystic duct. According to Ivy (36) two types of cells have been described and it has been postulated that the columnar cells have a secretory function while the slender elongated cells serve an absorptive function. It has also been postulated that these are merely different phases of the same cell, the main function being one of secretion and the slender elongated cells are merely columnar cells which have just emptied. Lymphatics are present in the subepithelial layer but do not extend up into the folds or rugae. Since substances must pass through considerable stroma to get to the lymphatics it is probable that most absorbed material passes directly into the blood stream.

The cystic duct runs from the collum of the gallbladder and joins the hepatic duct at an acute angle to form the common bile duct (ductus choledochus). The mucous membrane is thrown into spirally arranged folds which are a continuation of the apiral valve of the collum mentioned above.

The common bile duct (ductus choledochus) is formed by the junction of the cystic and hepatic ducts. It passes down, traverses the duodenal musculature obliquely and empties into the lumen of the duodenum. At its termination it lies in contact with the pancreatic duct which enters it in the region of the ampulla (of Vater). Therefore, they open by a common orifice on the summit of the duodenal papilla.

Newman (55) describes the musculature of the extra-

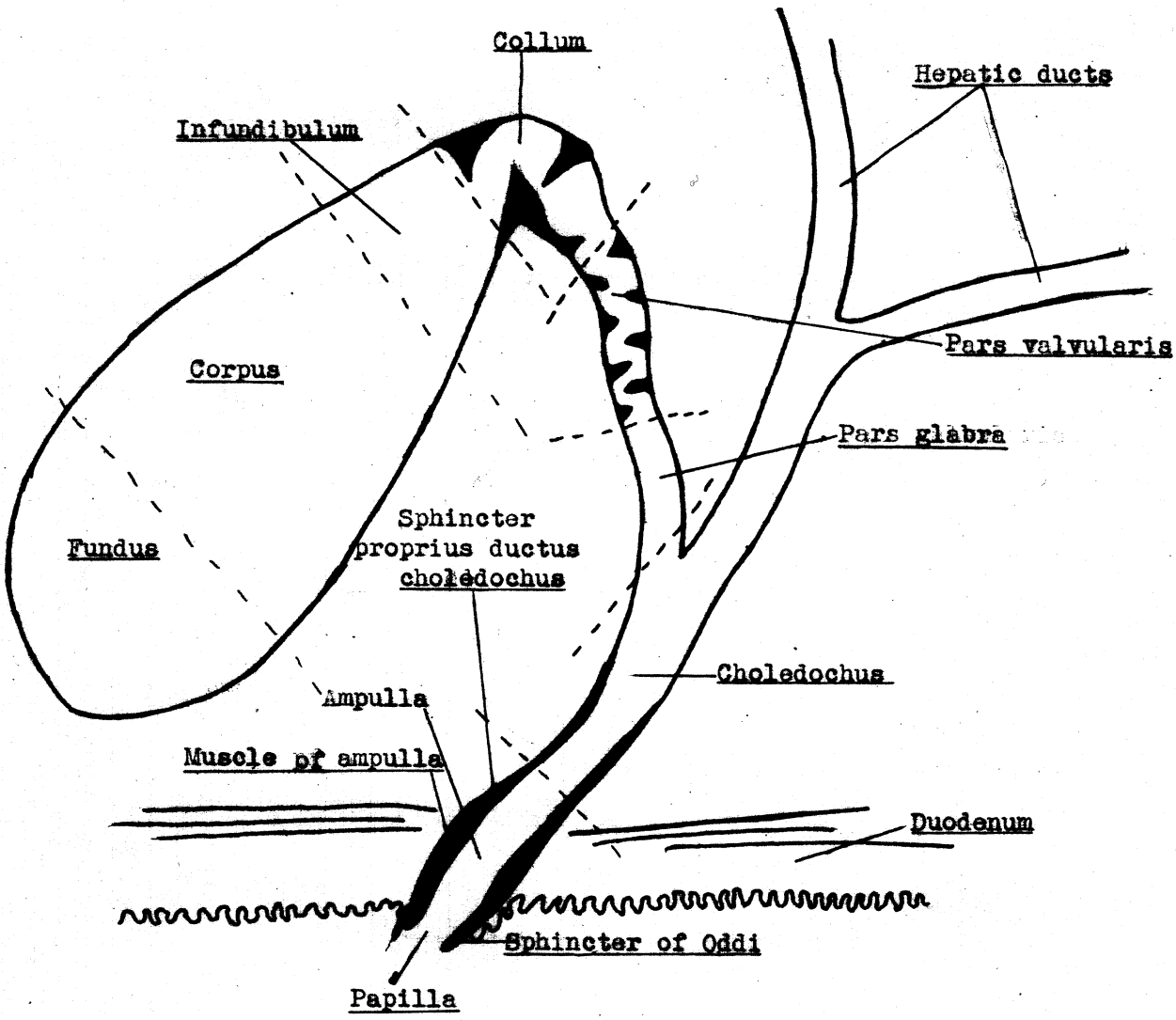
hepatic biliary system as follows. Smooth muscle is found mainly at the two ends of the gallbladder. There is a good deal in the fundus and much less in the body. The fibres are arranged longitudinally and obliquely. Much elastic tissue is present in the body with much less present in the muscular fundus and infundibulum. The muscle in the infundibulum is more circularly arranged and persists into the neck and valvular portions of the cystic duct. This may have a peristaltic or sphincteric action. Heister's valves have some circular muscle fibres. The rest of the cystic and all of the hepatic and the common duct to the ampulla are fibroelastic tubes with very little muscular tissue. In the ampulla the smooth muscle tissue reappears and is thicker than in other parts of the extrahepatic biliary tract. Also described by Berg (4). The fibres in the upper or intramural part are obliquely and longitudinally arranged. A circular ring of muscle tissue surrounds the duct in the tip of the papilla (sphincter of Oddi). This sphincter was described by Oddi (57) in 1887. It has also been described by others (34,49,66, etc.)

A sphincteric mechanism located just proximal to the ampulla termed the sphincter proprius ductus choledochus has been described by some authorities (36,37,77, etc.) based on anatomical and physiological evidence. Westphal (77) concluded that the sphincter of Oddi had a twofold structure, a muscular coat where the common duct joins the ampulla and a bundle of circular muscle fibres distal to this surrounding the papilla.

Giordano and Mann (31) state that a sphincteric mechanism is definitely present at the duodenal end of the common bile duct and this probably represents a true sphincter. Boyden (13) studied the phylogeny of the sphincter choledochus. He concluded that the sphincter of the common bile duct in the higher mammals represents a vestige of the intrinsic musculature of the extrahepatic biliary tract. In lower forms evacuation of the bile was accomplished by peristaltic movements from the gallbladder to the duodenal orifice. But in the human embryo the homologous muscular structure has been drawn into the duodenal wall during the fetal stages and remains as the principal mechanism by which bile is retained. Similar evidence submitted by Schwegler and Boyden (66).

Some authorities take the position that what has been described as a circular band of muscle fibres at the distal end of the common duct is simply duodenal muscle fibres encircling the ducts. In the guinea pig a definite ampulla is present with a sphincter proximal to it, sphincter proprius ductus choledochus, and a sphincter distal to it, sphincter papillae (of Oddi). In some lower animals the ampulla is external to the duodenal wall and the musculature is therefore distinct from that of the duodenum (36,13). In some cases of cholecystitis and peptic ulcer, the sphincter muscle is definitely hypertrophied (37, etc.).

The presence of a sphincteric mechanism located at the junction of the gall bladder and the cystic duct has also been postulated (36,37,39,45, 55,64). The presence


Collum
Hepatic ducts
Infundibulum
Pars valvularis
Corpus
Pars glabra
Fundus
Sphincter
proprius ductus
choledochus
Choledochus
Ampulla
Muscle of ampulla
Duodenum
Sphincter of Oddi
Papilla

of these various sphincters has been debated pro and con for many years. Many authorities have tried to assign a peristaltic rather than a sphincteric action to some of them.

I feel that at the present time, we might assume the following. There may or may not be a muscular sphincter located at the junction of the gallbladder with the cystic duct but there probably is not. The muscle fibres found in the valves of Heister are probably of very little physiological importance. The same may be said for any that may be found in the duct system proximal to the sphincter proprius ductus choledochus. There probably is a physiological sphincter located just proximal to the ampulla which has been termed the sphincter proprius ductus choledochus. The normal physiological function of the ampullary muscle is probably one of peristaltic action. There is probably a physiologically functioning sphincter located at the tip of the papilla which is termed the sphincter of Oddi.

PHYSIOLOGY

The physiology of the gallbladder was thoroughly reviewed in detail by Ivy (36) in 1934 and the reader is referred to that work for a comprehensive bibliography and a detailed presentation of the knowledge to that time. I have attempted to go back to only a fraction of the original articles on physiology and those will be presented in this paper.

The hepatic bile which enters the gallbladder is concentrated about ten times by this organ. The conc-

entration activity ceases when the total solids reach about 20-25%. (55,36).

Newman (55) feels that early water is absorbed and later the chloride is absorbed at a greater rate. Ivy (36) feels that sodium, chloride, bicarbonate and water are absorbed at the same rate and water is absorbed at the rate of about 6 c.c. per hour.

The gallbladder seems to conserve alkali since during absorption and concentration the pH of the bile changes from about 7 to 8.5 to about 5.2 to 7. There is an increase in acidity. (55,36). Acidosis or alkalosis has no relation to stone formation, and the acidity of the bile is not affected by the ingestion of acid or alkali by mouth (55).

Newman (55) states that calcium is concentrated in the gallbladder and calcium is secreted by the gallbladder only when the cystic duct is obstructed. Ivy (36) states that calcium absorption by the gallbladder is so slow that the final effect is one of concentration. When the gallbladder is slightly damaged calcium is absorbed faster than water and the concentration is decreased; when the gallbladder is damaged so that fluid flows into the gallbladder from its mucosa calcium is excreted; when the gallbladder is damaged so that water is not absorbed calcium is deposited in the submucosa.

The absorption of bile pigments is neglible and as a result they are concentrated (36,55).

Bile salts may be absorbed by the normal gallbladder and inflammation or irritation of the mucosa increases the rate of absorption. The normal gallbladder absorbs rel-

atively small amounts of cholesterol if any and the inflammed mucosa, because of its cholesterol content may add cholesterol to the bladder contents by desquamation or effusion (36,62). Newman (55) believes that the bile salts hold the cholesterol in solution by the formation of a water soluble addition compound. He feels there is an active absorption of the addition compound and bile salts but states that this doesn't jeopardize the solubility of the cholesterol. He states that as the acidity increases the bile salt decreases but that this is a buffering effect and is not significant in the formation of stones. He also feels that cholesterol is not absorbed by the gallbladder wall to any appreciable extent.

Fats, lecithins and soaps are secreted by the liver and only concentrated by the gallbladder (55).

Atropine doesn't prevent normal absorption or concentration. Peripheral vagus stimulation increases the rate of concentration while stimulation of the splanchnics decreases the rate of concentration. The effect may be due either to motor activity or to vascular changes. Gallbladder absorption in man may vary under nervous influences. (36).

Glands at the upper end of the gallbladder form a mucoid secretion which is probably true mucin. Albumen and globulin are not present and are not secreted by the bladder. (36,55).

The bile ducts instead of concentrating the bile dilute it slightly with a thin colorless secretion devoid of cholates even in presence of marked jaundice.

Filling of the gallbladder is dependent upon three factors, the secretory pressure of the liver, resistance to the flow of bile into the duodenum and the ability of the gallbladder to be passively distended.

Winkelstein and Aschner (80) believe that experimental evidence indicates that the muscle power of the gallbladder is not sufficient to cause emptying of the viscus. Copher et al (21) were never able to demonstrate rythmic contractions due to the musculature. On the other hand Ivy (36), Newman (55) and Boyden (11) feel that the muscle and elastic tissue present in the wall of the gallbladder is sufficient in quantity to allow for active contractions.

Active gallbladder contractions have been observed by direct visualization and by fluoroscopic studies and have been recorded by graphic records in response to mechanical, chemical, nervous and electrical stimuli. The consensus of opinion is that contractions occur with or without the administration of various drugs. (36,59).

In general four possible mechanisms of excitation of the gallbladder musculature have been suggested.
1. Local stimulation. Ganglia are present in the wall of the gallbladder and that they or the muscle fibres may be excited to initiate gallbladder contractions is suggested by the following. Distention of the gallbladder may cause contraction of the isolated gallbladder or the gallbladder in situ. A certain optimum tension is required for a maximum gallbladder response to stimuli;

hyperemia augments tone and anemia causes relaxation. Spontaneous tonic contractions may and do occur in the isolated gallbladder or in the gallbladder in situ. Strong irritants may cause the gallbladder to contract. Spontaneous tonic contractions without apparent cause do occur. The gallbladder empties when distended even during fasting (55). The normal gallbladder in a fasting individual or one on a carbohydrate diet may go five days or longer without evacuating (71). (36).

2. Reflex inhibition and excititation, from the gastro-intestinal tract. It has been demonstrated in lower animals that stimulation or irritation of the gastro-intestinal tract may reflexly increase or diminish gallbladder contractions. In general stimulation in the region of the duodenum and below to the rectum results in reflex inhibition of the gallbladder. The cecum is most sensitive for pain and for gallbladder inhibition. This lead to the attempt to correlate certain diseases of the gut such as peptic ulcer, appendicitis, colitis and constipation with gallbladder disease. (9,15) However, this has not been borne out in human. Rather it is thought to be not true (17). Experimental evidence indicates that duodenitis or duodenal ileus interferes with the flow of bile into the duodenum (38,55,67). also 22 It has been suggested that constipation might reflexly interfere with gallbladder evacuation (37,45).

3. Nervous reflexes from the cord and higher centers. Weak stimulation gives contraction of the gallbladder, peristalsis in the ampulla, relaxation of the sphincter of Oddi and evacuation. Strong stimulation gives

spasm of the gallbladder and ampulla and the flow of bile is prevented. The vagus also carries excitatory-secretory and inhibitory-secretory nerves to the liver (72). Parasympathetic drugs (histamine, pilocarpine, acetylcholine, morphine, ergotamine, etc.) contract the gallbladder. Stimulation relaxes the gallbladder and ampulla and contracts the sphincter of Oddi when the sympathetics are stimulated. Cutting the splanchnics increases the tonus rythm. Atropine relaxes the gallbladder by paralyzing the vagus. (36,37,39,46,55,55,77). Psychic factors such as perception of food or fear, anxiety and pain have been observed to cause gallbladder contractions with evacuation in both animals and humans (26,36). Since such a phenomenon must depend on nervous reflexes, it is apparent that a nervous control of the gallbladder must function and it is not impossible that psychic or emotional factors might alter the function of the extrahepatic biliary tract for better or for worse. Bartle (3) states that afferent impulses incoming in over the fifth nerve reach the nucleus which is in the region of the nucleus of the tenth and in close apposition with it. He concludes that affections of the head may influence gastro-intestinal function by setting up abnormal stimulation of the vagus nerve.

4. Humoral agents. Humoral agents may be of two kinds, a specific hormone or products of food digestion. Ivy (36) states that from the evidence at hand it does not appear likely that post absorptive substances from the digestion of ingested food are concerned in the contraction of the gallbladder and its evacuation. Exper-

imental work quite definitely shows that a substance which may be extracted from the duodenal musculature with dilute hydrochloric acid, cholecystokinin, is regularly effective in initiating gallbladder contraction and evacuation. It is probable that it is the physiological stimulus for gallbladder evacuation.The formation of this substance is not definitely understood, but it is probably due to the action of the products of fat digestion upon the duodenal mucosa. A little cholecystokinin may be produced in the stomach. It has been suggested that egg yolk, olive oil, cream, butter,etc., through their digestive products lead to the formation of cholecystokinin. Undigested egg yolk and olive oil apparently produce no cholecystokinin. Bile may flow when the duodenal contents are alkaline and yet may not flow when the duodenal contents are acid. (36,37,42,55,71). Fats and fatty acids act to empty the gallbladder most effectively. Meats (proteins) will cause gallbladder evacuation but are not nearly so effective as fats. Of the peptones, meat is the best for promoting evacuation. Egg white and casein are practically without effect. All carbohydrates are comparatively ineffective. The drinking of water or the intraduodenal introduction of warm water has been observed to initiate some evacuation of the gall bladder. (36).

Reports vary as to the effectiveness of dilute hydrochloric acid in the duodenum. Some report that the flow of bile has stopped or the sphincter has gone into spasm after the intraduodenal administration of hydrochloric acid (1,24). But the greater number describe a

moderate contraction of the gallbladder and a flow of bile (36,31,15). The gallbladder does not respond to the administration of egg yolk below the level of the jejunum. A response has been observed after gastrectomy, gastro-jejunostomy and after gastro-enterostomy when the duodenal secretion was drained into the lower ileum. It is therefore not necessary for the egg yolk and cream to pass through the duodenum to produce gallbladder contractions. (36).

The normal gallbladder in a fasting individual or in one on a carbohydrate diet may go five days or longer without evacuating (71).

Copher, Kodama and Graham (21) and Winkelstein and Aschner (80) thought intra-abdominal pressure changes effected the filling and emptying of the gallbladder. Ivy (36) states that the statement is warranted that changes in intra-abdominal pressure play no role in the evacuation of the gallbladder; under certain abnormal conditions, slight evacuation may occur concomittantly with sudden changes in intra-abdominal pressure but the evacuation can't be due to an uncomplicated rise in intrapabdominal pressure for physical reasons. Newman (55) agrees with Ivy on this. The fact that the gallbladder cannot be emptied by respiratory or other voluntary muscular movements is self evident if physical laws of pressure are understood since changes in intra-abdominal pressure are transmitted to the lumen of the duodenum even as they are to the lumen of the gallbladder.

The flushing action of the hepatic bile as suggested by some authorities (21,80) must play a very minor if

any role in the evacuation of the gallbladder as is seen if the rapidity with which the hepatic bile is concentrated and the relatively rapid emptying of the gallbladder in the early phase is considered (36).

It is noted elsewhere that the gallbladder will empty spontaneously at times and it is thought that this is due to distention or to a stretch stimulus. But that this is the prime method of emptying as believed by some (21) is quite definitely not true. A more correct interpretation is to say that the gallbladder will empty more effectively to a stimulus if the muscle fibres are under an optimal tension. (36).

It has not been shown that during digestion there is enough change in liver volume to account for the evacuation of the gallbladder and if there was one would not expect specific changes with specific foods. Since the isolated gallbladder is capable of producing a pressure of about 80 m.m. less than the gallbladder in situ, Ivy (36) concludes that not more than this amount can be laid to change in liver volume. (36). Evidence has been presented to show that the gallbladder does not empty by elastic recoil alone. When the common duct is cut and left open in the abdomen, it doesn't empty unless it is stimulated by a fat meal. If it is overdistended, it can empty by elastic recoil. (55).

In view of the mass of evidence at hand gravity need not be seriously considered. Ivy (36) points out that at one time gravity was thought to be an important factor in the emptying of the stomach. Not only is it reasonable to assume that siphonage is impossible because of

the collapsibility of the walls of the ducts, but siphonage has been ruled out by experimental work. (36).

While it is conceivable that peristaltic waves of the duodenum might influence the egress of the bile from the common duct, it is not logical to assume that this is the major mechanism in view of the other evidence presented and also since the walls of the ducts are not sufficiently rigid to allow for such a mechanism (36). It has been shown that the gallbladder may contract and evacuate when separated from the miling action of the duodenal musculature (36). All observers accept the fact that duodenal motility and tone play a part in the control of the flow of bile into the duodenum (36). But it has been observed that bile may be expelled at times without relation to discernible duodenal peristalsis or peristalsis may be present without the expulsion of bile as with a barium meal or carbohydrate meal (31,36, 37). The gallbladder when damaged by cholecystitis or trauma does not evacuate indicating that duodenal motility and other factors are of minor importance. It may be said that in the absence of activity of the gallbladder musculature, the gallbladder either does not evacuate or is not evacuated normally by the accessory factors which may exist. Newman (55) agrees with the above. Copher, Kodama and Graham (21) and Burget believe that duodenal tone and peristalsis are effective factors in the evacuation of the gallbladder.

During evacuation the gallbladder rises, stiffens and becomes oval in shape. The fundus contracts or the whole gallbladder may contract at once. Contraction

rings have been seen. The intrabiliary pressure rises to 200 to 250 c.m. of bile. Simultaneously there is a lowering of resistance to the flow of bile into the duodenum. The bile emerges in spurts and gushes. The spurts may occur with a wave of duodenal peristalsis but they have also been observed to occur between waves. No doubt the muscle of the ampulla can work quite independently of the duodenal wall contractions. Meltzer's law of reciprocal innervation is thereby confirmed. Newman (55) believes that the gallbladder by contraction feeds the bile to the ampulla which acts to expel it into the duodenum by means of peristaltic contractions. (55).

The gallbladder does not contract in one single and complete wave as does the urinary bladder but undergoes intermittent contractions (11,12). There are two general phases of contraction and the first phase is divided into three parts. In phase I thereis an initial response which follows a latent period of about one minute after the taking of food and it is completed in two minutes. It is probably due to a cephalic or psychic reflex relaxation of the sphincter and contraction of the gallbladder or due to the passage of food into the stomach or duodenum. The initial response is followed by a two minute pause during which the gallbladder fills slightly or ceases its discharge due probably to a return of the sphincter to its original tone. Then follows the principal period of discharge lasting on an average of 32 minutes during which one-half to three-quarters of the gallbladder contents are evacuated (11, 12). Following the first phase of contraction there is

a period of rest lasting 5 to 45 minutes. Then phase II follows which may be followed by other phases until the gallbladder is practically emptied of its contents. The later phases are not as sharply defined as the first and the gallbladder is not distended, the muscle is less effective and evacuation is more slow. Occasionally the gallbladder may completely refill between phase I and phase II in which case complete evacuation occurs during phase II. (Boyden,12).

Three types of response of the human gallbladder to a stimulus have been described. In type I the stimulus results in an initial relaxation of the gallbladder with an apparent simultaneous closure of the sphincter. This is rare and results in only a temporary delay of evacuation. In type II the stimulus results in contraction of the gallbladder and probably a simultaneous relaxation of the sphincter. Evacuation follows at a rapid rate. In type III the initial phase of emptying is followed by filling and the time of evacuation is prolonged. The sphincter and not the gallbladder is proably responsible. (Ivy,36).

Certain indirect evidence has been presented favoring the theory of the presence of a sphincter of Oddi. After cholecystectomy, the extrahepatic bile ducts and the stump of the cystic duct dilate but not to the degree found in malignant obstruction. If the sphincter of Oddi is destroyed no dilatation takes place. (36,37,38, 39,41,55). The flow of bile changes from a spurting to a dribbling form of discharge resembling a sort of retention overflow and the intrabiliary pressure falls.

Judd and Mann (41) have suggested that the ducts may dilate because the sphincter attempts to maintain the difference between the rate of secretion and the rate of discharge and bile accumulates in the biliary tract. In some cases where the ducts dilate, the incontinence disappears(36). In others the incontinence or dribbling persists and the ducts don't dilate. Perfusion pressure has been shown to increase immediately following cholecystectomy (59) and it has been shown to fall following cholecystectomy (41). Ivy (37) believes that the incontinence of the sphincter following cholecystectomy demonstrates that the gallbladder has a functional relation to the sphincter. Puestow (60) found that both dilatation of the common duct and pernanent loss of function followed cholecystectomy. From the varied reports above it may be seen that there appears to be no constant relation between function of the sphincter, dilatation of the ducts and intrabiliary pressure. It is impossible to prognosticate what the effect of cholecystectomy will be by correlating the above reports. It is interesting to note that in those animals which have no gallbladder the bile flow into the duodenum is also of the continuous dribble type (36,55). A sphincter is present irrespective of the presence of a gallbladder but in those animals without a gallbladder the muscle fibres appear more as interlacing fibres of duodenal muscle and less like a separate entity (55).

Increasing the tone of the duodenum retards the flow of bile into the duodenum while decreasing the tone of the duodenum and promoting normal peristalsis favors

the flow of bile into the duodenum (37). Some authorities state that the resistance is due entirely to pressure exerted on the duct by contraction of the duodenal musculature as the duct traverses the duodenal wall obliquely (36,37). Others report that the resistance is due to the action of a sphincteric mechanism independent of the duodenal wall. The common duct has been freed from the duodenal musculature and on electrical stimulation, the flow of fluid was obstructed by a constricted area corresponding to the sphincter proprius ductus choledochus and the resistance offered was greater than the pressure of bile secretion or the pressure of a gallbladder contraction (34). It has been shown that drugs which contract the duodenal musculature also increase intramural resistance and this has been used as an argument for the absence of a sphincteric mechanism, the resistance being due to duodenal tonus. But this is not always true. That is, intramural resistance may be increased when the duodenum is relaxed and vice versa. (36,46).

Burget (18) by a rather ingenious operation removed the factor of the sphincter of Oddi. After this he found that the intrabiliary pressure was normal, the gallbladder filled and emptied normally and the response to various drugs was the same as when the sphincter was present. From this work he assumed that the tonicity of the duodenal musculature when the common duct traverses it obliquely contitutes a sphincter like mechanism to prevent the continuous flow of bile in the presence of a gallbladder. He also assumed that the bile flow is

regulated by intra-abdominal pressure and tonicity and by peristalsis of the duodenum. He denied the existence of a reciprocal activity between the gallbladder and a sphincteric mechanism that would influence the flow of bile.

Giordano and Mann (31) observed bile discharging in intermittent spurts without duodenal peristalsis. They stated that if peristalsis is present bile discharge into the duodenum can occur only with peristalsis and they concluded that the discharge of bile into the duodenum is modified by and to some extent is dependent on peristalsis.

Lueth (46) showed from experimental work that the physiological sphincter surrounding the duct in the papilla exerts from 1/3 to 1/6 of the total intramural resistance. Drugs in general influence the tone of the intramural resistance and the tone of the duodenum in the same way but not invariably.

Ivy (36) states that all observers accept the fact that duodenal motility and tone play a part in the control of the flow of bile into the duodenum. This has been graphically demonstrated. But visual observations indicate that bile may be expelled at times without relation to discernible duodenal peristalsis or peristalsis may be present without the expulsion of bile. Bile may spurt from the papillary orifice without evident peristalsis, but if peristaltic waves are present, the outflow will occur with the peristaltic wave. In those species which possess a gallbladder, the common duct possesses a special sphincteric mechanism which is in-

timately coordinated with duodenal tone and peristalsis, but which may also function independently.(36,37)

Westphal (77) first demonstrated that weak stimulation of the vagus gives contraction of the gallbladder, peristalsis in the ampulla, relaxation of the sphincter of Oddi and evacuation; strong stimulation of the vagus gives spasm of the gallbladder and ampulla and bile flow is prevented; stimulation of the sympathetics relaxes the gallbladder and ampulla and contracts the sphincter of Oddi; cutting the splanchnics increases the tonus rythm. This is accepted by (36,37,39,46,55).

The vagi exercise a tonic motor control over the musculature surrounding the intramural portion of the common duct and stimulation of the peripheral vagus may increase or decrease intramural resistance irrespective of duodenal tone but the usual effect is contraction of the duodenum and increase of intramural pressure.(37, 46). It has been demonstrated in lower animals that stimulation of the vagus results in increased duodenal tone and relaxation of the papillary portion of the sphincter while stimulation of the sympathetics has the opposite effect(36).

Experimentally chemical irritation of the duodenum can prevent gallbladder contraction apparently by causing spasm of the sphincter (38,22). A duodenitis or duodenal ileus interferes with the flow of bile into the duodenum (38,55,67).

There is probably a sphincteric mechansim present which may act independently of the duodenum, but it is intimately connected with duodenal tone and motility. It

is located in theintramural portion of the common duct and in the papilla. (5,6,7,13,26,34,36,37,38,39,40,55, 77,etc.)

Meltzer (49) suggested that there may be a general physiological principal termed the law of contrary or reciprocal innervation which functions in other systems of the body and might be applicable to the gallbladder-sphincter system, and he suggested that it might play a leading part in the discharge of bile. Winkelstein and Aschner (80) and Burget (18) deny the existence of a reciprocal innervation or mechanism between the gallbladder and the sphincter mechanism. But the theory of a reciprocal innervation is now generally accepted and has been demonstrated to exist between the gallbladder and the sphincter. Normally when the sphincter contracts the gallbladder relaxes and when the gallbladder contracts the sphincter relaxes.(15,31,36,37,53,55,77,etc.)

Ivy (36) believes that the pressure regulatory function of the gallbladder is its most important function. It regulates pressure by means of its elastic distensibility provided by the elastic muscle fibres in its coat and by its remarkable absorptive and concentrating ability it provides for the continuous secretion of bile by the liver cells and allowes for storage of most of the liver bile. By means of this pressure regulatory mechanism it provides for the continuous but varying rate of bile formation. The gallbladder when it contracts doesn't normally exert a pressure greater than the secretory pressure of the liver. Cantarow (20) points out the serious consequences of the presence of

an intrabiliary pressure greater than the secretory pressure of the liver. It results in sever damage to the liver substance. Following cholecystectomy the ducts dilate, the choledochal-duodenal resistance decreases or both. With any obstruction to the common duct, jaundice is hastened and liver damage occurs more promptly. It is obvious that an important factor of safety has been lost when cholecystectomy is performed. (36).

Acting in a similar manner the gallbladder functions to store bile for the purpose of digestion. The propulsive force of the gallbladder serves to assist in the evacuation of bile at the time when bile is needed in the digestive processes. The concentrated bile which it supplies serves in the digestion and aborption of fats and increases bile formation. (36). The fact that digestion is not impaired following cholecystectomy is no argument against the above. It cannot be overlooked that the gallbladder acts as a factor of safety. These principles should be considered "before the gallbladder is to be viewed as a surgical trophy". (36). The day of "prophylactic" cholecystectomies should be over.

The sphincter or intramural mechanism is necessary for filling of the gallbladder and for the storage capacity of the gallbladder and it prevents the regurgitation of the duodenal contents into the common duct. (36, 37,54,80).

The valves of Heister may act as support to prevent the collapse of the cystic duct. It is known that there is some impediment to the flow from the gallbladder into the common duct and from the common duct into the

gallbladder as a certain latent period has been observed in pressure changes on either side of the cystic duct. It is possible that these valves offer only enough resistance to flow to prevent any sudden changes in pressure or rapid exchange of contents. (36,45,64).

The secretory pressure of the liver has been given as being from 240-310 m.m. of water in the dog and from 210-270 m.m. of water in the human (36,37,38), but it seems to be generally considered to be about 300 m.m. of water (37,39,53). The gallbladder contraction pressure has been reported as being from 240-250 (36) and even as high as 300 m.m. of water (36). Some over 250 m.m. of water pressure would probably be a fair figure. It has been reported that the sphincter may resist a pressure of from 100-120 m.m. of water when resting (26); it rises to from 240-720 m.m. of water pressure during fasting (26) and may resist a pressure of well over 750 m.m. of water up to 800-900 m.m. of water or more when spastic. The intrabiliary pressure is normally about 100 m.m. of water but may rise to 200-250 m.m. when fasting(26). (36,37,38,39,53,55).

With a sphincter resistance of 600 m.m. of water pressure or more and a gallbladder contraction pressure of 200-250 m.m. of water it is evident that the gallbladder may contract without emptying in the presence of a hypertonic sphincter or a hypertonic sphincter can prevent gallbladder contraction (37,38,39). Normally the gallbladder pressure never equals the secretory pressure of the liver (37,38).

Pain may be produced if the intrabiliary pressure rises to a sufficient height due to the contraction of

the gallbladder against a spastic sphincter, or the secretory pressure of the liver is sufficient to produce pain when the common duct is obstructed particularly if the pressure is exerted suddenly. (24,37,40,73,77). Pain has also been noted following the injection of cholecystokinin when the cystic duct was obstructed (19, 39,40,51,52,73,74,75).

BILIARY DYSSYNERGIA

Dyskinesia is derived from two Greek words meaning bad and movement. Biliary dyskinesia is a functional disorder of the gallbladder and bile duct motility and tonicity. (45).

Many terms have been applied to the same state of functional disorder, physiologic block, cholepathia spastica, spastic distention, atonic distention, hypertonic dyskinesia, static gallbladder, etc. Some of these terms refer to one or the other of the two states which together make up the syndrome of dyskinesia. Best and Hicken (5,6,7,8,33) coined the phrase "dyssynergia" for the same pathological state believing it to be more descriptive and more appropriate. Throughout this paper I have made no attempt to differentiate between the two terms and have used them interchangeably as is proper since they possess identically the same significance.

Vesalius in 1543 called attention to the membranes that prevent the regurgitation of the duodenal contents into the common bile duct, to the tortuousness of the entrance of the duct into the intestine and to some impeding flow from the orifice. Claude Bernard demonstrated a spurt of bile when dilute hydrochloric acid was

dropped on the papilla and suggested that the ampulla contracted. (14).

In 1679 Gage (29-A) described the muscle fibres encircling the ampulla of the common duct in the cat.

Oddi in 1887 (57) demonstrated circular muscle fibres surrounding the common bile duct and was the first to measure the resistance of the sphincter. He demonstrated that the removal of the gallbladder resulted in the dilatation of the bile ducts and suggested that a dysfunction of the sphincter might explain certain morbid dysfunctions of the biliary tract with symptoms similar to those of biliary colic.

In 1903 Krukenberg (44) described a case of typical gallstone colic which showed neither claculus nor infection at operation. This was the so-called "gallstone colic of Krukenberg".

In 1909 Aschoff and Bacmeister (2) used the term "static gallbladder" to describe those cases where operation disclosed no stones, inflammation, strictures or kinks to account for biliary colic and no condition of the gallbladder wall which had so affected its muscular structure as to interfere with its normal motility.

Borghi in 1913 (10-A) also observed cases of gallstone colic without pathological evidence to explain it. Judd and Mann in 1917 (41) called attention to the importance of a choledocho-duodenal sphincter mechanism and observed that when the muscle fibres of the sphincter were dissected out dilatation of the ducts did not occur after cholecystectomy. In the same year Meltzer(49)

theorized that there may be a general physiological principal termed the law of contrary or reciprocal innervation which functions in other systems of the body and might be applicable to the gallbladder-biliary system. He thought it might play a leading part in the mechanism of the discharge of bile and a disturbance of the fine adjustment might be a pathogenic factor in many biliary disorders. He suggested that emotional factors or dietary indiscretions might lead to biliary stasis or emotional jaundice. He observed that magnesium sulfate when applied intraduodenally exerts a relaxing effect on the sphincter mechanism and suggested that such a procedure might permit the passage of bile or even a calculus of moderate size.

Archibald (1) in 1919 basing his work on experimental and theoretical observations in regard to a spasm of the sphincter of Oddi was successful in producing pancreatitis. He used dilute hydrochloric acid in the duocenum to throw the sphincter into spasm after which he suddenly injected bile into a cannula fastened in the common duct in the hope that some bile might be driven up the duct of Wirsung in the presence of a spastic sphincter. His hopes were realized inasmuch as he was successful in repeatedly obtaining gross and microscopical evidences of pancreatitis. It is interesting that he was successful in producing a spasm of the sphincter by the use of dilute hydrochloric acid as this is generally thought to act to relax the sphincter. Doubilet and Colp (24) in 1937 also observed that dilute hydrochloric acid causes a temporary spasm of the sphincter.

Schmieden (64) in 1920 used the term "stasis of the gallbladder" in those cases in which operation failed to reveal any cause for pain in those patients who had manifested typical symptoms of gallbladder colic. He attributed the distress to the distention of the gallbladder which was present and he attributed the distention of the gallbladder to a spastic mechanism which prevented the free flow of bile from the gallbladder into the cystic duct. Ivy (37, 39) and Lipschutz also feel that a sphincter mechanism located in the neck of the gallbladder may interfere with with the flow of bile under abnormal conditions.

Smithies, Frank, Karschner and Oleson (69) in 1921 described a " physiologic block" with a lack of bile flow in the face of an absence of organic cause when doing duodenal drainages. They found it more frequently in excitable and apprehensive Latin Americans or psychically hyperplastic Jews. In 1922 Berg (4) conceived the idea of a possible relation between biliary stasis and a functional disturbance of the bile ducts or spasm of the sphincter of Oddi. He noted in certain cases that muscle fibres which encircled the ampulla of the common duct were hypertrophied.

Potter and Mann (59) noted that intrabiliary pressure varied with different diets. Intrabiliary pressure was highest with a milk diet, intermediate with a dog biscuit diet and lowest during fasting. 1926.

In 1927 Giordano and Mann (31) stated that a sphincteric mechanism is definitely present at the duodenal end of the common bile duct and that this probably represents

a true sphincter. They suggested that this sphincteric mechanism might be thrown into spasm by a pathological condition of the gastro-intestinal tract and the adjacent organs and some cases of jaundice and pancreatitis might be explained on the basis of this spasm. They observed hypertrophic changes in the sphincter associated with peptic ulcer and cholecystitis. Newman (55) has also demonstrated a hypertrophy of the sphincter following cholecystectomy in dogs.

Westphal (77) by animal experimentation worked out a clear cut conception of the disorders of the motility of the gallbladder and its ducts. He concluded that the sphincter of Oddi had a twofold structure, a muscular coat surrounding the antrum where the common duct joins the ampulla and a circular bundle of muscle fibres distal to this surrounding the ampulla. In response to stimulation of the vagus with a weak faradic current the gallbladder contracted, the papilla relaxed and peristaltic movements were seen in the antral portion of the sphincter. He concluded this was the normal response. In response to a stronger current there was a marked increase in the tonus of the gallbladder muscle and greater peristaltic activity in the ampulla. This probably corresponds to what will be discussed later as hypermotile dyskinesia. Using a still stronger current he observed a violent contraction of the gallbladder with spasm of the sphincter. The spasm was painful due to the associated distention. This probably corresponds to what will later be discussed as hypertonic dyskinesia.

He further observed that faradic stimulation of the sympathetic or splanchnic nerves reverses these processes; the antral portion of the sphincter relaxes as does the gallbladder itself, while the sphincter of Oddi contracts. Sympathetic stimulation apparently doesn't cause pain and it probably corresponds to the atonic type of dyskinesia. Westphal classified his types of dyskinesia as below.

I Hyperkinetic Dyskinesia	II Atonic Dyskinesia
A.Hypermotility--contraction of the gallbladder and peristalsis of the ampulla are increased with resulting rapid evacuation of gallbladder contents.	Atony or relaxation of the gallbladder and spasm of the sphincter of Oddi result in atonic distention of the gallbladder attended by a dull, heavy, aching sensation or a sensation of tumor.
B.Hypertonicity--Strong contraction of the gallbladder against a spastic sphincter interferes with emptying and is accompanied by spastic distention and colicky pain.	

Lueth (46) in 1931 corroborated Westphal's findings. He concluded that a sphincter mechanism is present in the intramural portion of the common duct and in the papilla which is intimately coordinated with duodenal peristalsis but may function separately. The vagi exercise a tonic motor control over the musculature surrounding the intramural portion of the common duct and stimulation of the peripheral vagus may increase or decrease intramural resistance but the usual effect is contraction of the duodenum and increase of

intramural resistance. The physiological sphincter surrounding the duct in the papilla exerts from 1/3 to 1/6 of the total intramural resistance. Drugs in general influenced the tone of the intramural resistance and the tone of the duodenum in the same way. (46).

In 1933 Strauss, Strauss, Crawford and Strauss (70) reported a series of 22 cases of chronic bile retention which, on operation, showed only a duodenitis and inflammation of the ampulla of Vater to account for the symptoms. In the same year Ivy, Voegtlin and Greengard (40) while doing a duodenal intubation injected cholecystokinin. The expected flow of bile did not appear and the patient complained of increasing pain which was that of typical biliary colic. But when they administered magnesium sulfate by way of the tube the pain was immediately abolished and a flow of bile was obtained. They concluded that the lack of bile flow must have been due to a spastic sphincter and the pain was due to an increased intrabiliary pressure due to contraction of the gallbladder in the presence of a spastic sphincter of the common bile duct which resulted in an increase in intrabiliary pressure. The magnesium sulfate must have acted to relax the sphincter or the gallbladder or both.(40).

Ivy (36) and others (19,34) state that the gallbladder may contract with a pressure up to 200 to 300 m.m. of bile pressure while the intramural mechanism is capable of resisting a force of from 750 to 800 m. m. of water pressure which is sufficient to prevent gallbladder contraction. Therefore if the sphincter or

duodenum is hypertonic the gallbladder may contract without evacuating resulting in visualization of the hepatic ducts and may even cause biliary colic or jaundice if it persists. He states that bilirubinemia occurs in cholecystectomized dogs when the intraductal pressure reaches 200 to 350 m.m. of water. In fasting dogs the intramural resistance may reach as high as 200 to 250 m.m. of bile. This would suggest an explanation for starvation icterus or physiological jaundice which occurs after a 24 hour fast in most dogs and occasionally in man. (36). Normally the gallbladder pressure never equals the secretory pressure of the liver, 300 m.m. of water pressure (37).

Ivy (36,37) and Lipschutz (45) feel that the hyper tonic type of dyssynergia may be associated with a spasm of a sphincter located at the neck of the gallbladder. If this is true, one wouldn't expect the ducts to visualize during cholecystography.

In 1934 Ivy and Sandblom (39) stated that they believed a concept of biliary dyskinesia to be established and by means of this concept the following may be explained, typical symptoms of biliary tract disease without stones, inflammation or other pathology to explain it as described by the men noted above and many other clinicians, "hepatic neuralgia", normal visualization of a gallbladder without normal evacuation, predisposition to infection and stone formation and the recurrences of symptoms following cholecystectomy. They feel that there are two possible locations of the obstruction. If the obstruction is at the common duct sphincter the

gallbladder contracts and the ducts are visualized. If the obstruction is at the neck of the gallbladder annular contractions without evacuation may be seen. Walters and Thiessen (76) in the same year while working on another problem observed postoperative radiographic findings which suggested the possibility of a spasm of the sphincter.

In 1935 Best and Hicken (5) injected a radiopaque substance into a T-tube in place in the common duct after a cholecystectomy. By means of this cholangiography they were able to visualize the biliary ducts. They noted a dilatation of the common duct and of the intrahepatic radicals and an apparent obstruction at the lower end of the common duct which prevented the flow of fluid into the duodenum. They reasoned that since a duodenitis or inflammation of the ampulla must have resulted in an obstruction of a longer duration this must have been a sphincterismus or spasm of the sphincter.

Later Hicken, Best and Hunt (33) described five cases of biliary dyssynergia which they recognized by the location and the evanescent character of the obstruction and it was later proved at operation that no organic obstruction was present. They remarked that a functional derangement occurs more frequently than they had thought. Best and Hicken (7) reported spastic dyssynergia to be present in 15% of patients in a series of 75 cases of biliary tract disease but could not correlate it with the degree or type of gallbladder pathology. They were able to relieve the

symptoms of spastic dyssynergia with glyceryl trinitrate, magnesium sulfate, atropine, belladonna, cream and olive oil. They observed that the choledochal sphincter contracted as a rule under a spinal anesthesia and suggested that this might be due to release of the antagonistic balancing effect of the sympathetics which are lost with spinal anesthesia. (6,7).

Hicken and Best (6) believe that dyssynergia may account for some of the cases of postcholecystectomy pain. Puestow (60) who believes that most of this type of pain is due to organic obstruction is hardly disputing this since it is probably true that dyssynergia does not account for the majority of cases of postcholecystectomy pain.

Doubilet and Colp (24) in 1937 report that spasm of the common duct sphincter has been demonstrated in humans. They state that the ingestion of food does not cause relaxation of the sphincter in the absence of a gallbladder. They found that dilute hydrochloric acid causes a temporary spasm of the sphincter which may be relieved by atropine. They found that the effect of adrenalin on the sphincter to be negligible.

A spastic sphincter may cause biliary tract pain in the presence of a contracting gallbladder. This has been demonstrated following the injection of cholecystokinin (19,39,40,51,52,73,74,75,55); following the injection of pilocarpine when the gallbladder was contracting in response to a fat meal (37,40,77); and following the production of a pressure of from 150 to 300 m.m. of water (37). It follows that the secretory

pressure of bile (300 m.m. water pressure) when exerted suddenly on the bile ducts is adequate for the production of pain. (24,37,40,73,77).

Walters (73) showed that the pain of biliary tract disease is due to increased pressure and notes that postcholechystectomy pain may be due to stones in the common duct, recurrent pancreatitis and cholangitis and partial stenosis or inflammation in the region of the sphincter of Oddi. It has been demonstrated by manometric and cholangiographic studies that spasm of the sphincter may be produced by morphine and may be relieved by amylnitrite or nitroglycerine. The spasm is accompanied by pain and the pain is relieved when the spasm is relieved.

Bartle (3) brings out the fact that there are only two types of abdominal pain, that due to inflammation with involvement of the parietal peritoneum and that due to spasm or colic of smooth muscle. This fact is now quite widely accepted. Ivy (40) concluded that pain can be on a functional basis.

Bergh and Layne (81) produced pain in patients by distending the bile ducts with a pressure of 50 to 100 c.m. of water exerted through a T-tube which was in place following a cholecystectomy. If they gradually increased the pressure to 100 cm. of water no pain was experienced. All of the patients had deep epigastric and right upper quadrant pain identical with the pain previously experienced with their disease. Marked rigidity of the abdominal wall particularly of the hypochondrium was associated with the pain. Two of the

patients vomited and two of them belched.

McGowan, Butsch and Walters (52) took pressure readings from a T-tube in place after a cholecystectomy. They observed that morphine produced a rise in intraductal pressure and in one case this rise of pressure was accompanied by typical gallbladder pain. Lowering of the pressure and relief of the pain was obtained immediately with the administration of amyl nitrite. Glyceryl trinitrate had the same effect but to about 1/3 the efficiency of amyl nitrite.

Later (19,74,75) they demonstrated that morphine raises both the intraductal pressure and the sphincter resistance. Pantopon, dilaudid and codeine had the same effect to a lesser degree. Constriction of the sphincter was shown by roentgenograms. The spasm was relaxed by amyl nitrite, glyceryl trinitrate, theophylline with ethylenediamine but atropine and scopolamine did not relax the spasm following morphine. Relaxation of the sphincter was demonstrated by roentgenograms. They also noted a simultaneous spasm of the duodenum with the increase in intrabiliary pressure and perfussion pressure and with the spasm of the sphincter. Doubilet and Colp found that the spasm produced by morphine lasts over three hours and is not relieved by atropine (24).

If it is realized that morphine produces spasm by musculotropic action, it can be seen why atropine which acts to paralyze vagus action does not relieve the spasm produced by morphine and it can be seen that amyl nitrite, nitroglycerine, etc. which act directly on smooth muscle do relieve the spasm of morphine.

In 1938 McGowan, Knepper, Walters and Snell (51) reported that when they produced colic in patients who had undergone cholecystectomies by the use of morphine as they had done before (19,52,74,75) and as others had done , they noted that the second portion of the duodenum went into spasm which they demonstrated by manometric and radiographic findings. This spasm was accompanied in some cases by typical pain of biliary colic. And this spasm of the duodenum apparently involved the lower portion of the common duct. They demonstrated that patients with intractable postcholecystectomy colic not relieved by nitrites and presenting x-ray evidence of spasm of the third portion of the duodenum had the highest resting intraduodenal pressure. Patients who suffered from postcholecystectomy biliary colic which was relieved by nitrites had the lowest resting intraduodenal pressure. From this they concluded that spasm of the duodenum is a factor in biliary dyssynergia particularly in those cases suffering from intractable biliary colic and spasm of the duodenum alone might be sufficient to account for the symptoms. They showed in this work that the intraduodenal pressure of normal pressure to be intermediate between that of the two groups mentioned above.

In view of this and in view of the work of Lueth (46) and Burget (18) and the opinions of Ivy (36,37,38, 39) and others (55,80,31), we must not lose sight of the fact that some cases at least of functional biliary colic may be explainable on the basis of spasm of the duodenum alone. To differentiate between duodenal and

sphincter spasm by means of cholangiographic or cholecystographic studies would be difficult I believe. However, if pressure studies taken during duodenal intubation (McGowan et al (51) found that an open Sawyer tube gave as accurate readings as a closed system) or x-ray studies following a barium meal indicated that an increased tonus or spasm of the duodenum existed, I feel that one should be cautious before attributing all the symptoms to a spastic sphincter.

Newman (55) points out that dyskinesia of the biliary system is part of a dyskinesia of many organs.

It is almost axiomatic that functional derangement usually antedates and certainly predisposes to organic structural changes of the gastro-intestinal tract and its appendages. The common innervation from the vagus and the sympathetic systems would suggest a unity of functional disorders occuring with biological alterations of habitus. Much study has been given the functional disorders of the stomach, intestine and colon but scant attention has been given thus far as to its existence in the gallbladder and extra-hepatic biliary tract. (Lyon,47). Hicken, Best and Hunt (33) feel that since cardiospasm prevents food from entering the stomach, pylorospasm causes obstructive gastric retention, hypertonicity of the rectal sphincter initiates constipation and fecal stasis and a sphincterismus of the bladder neck interferes with micturition, it is not unreasonable to assume that the choledochal sphincter can by spastic contraction interfere with the free flow of bile into the duodenum. Bartle (3) says that the greatest number of

symptoms of the gastro-intestinal tract are surely those of disturbances of normal motility or interferences with normal peristaltic gradient. Among these may be mentioned nausea, vomiting, belching, regurgitation, heart burn, pylorospasm, distention, borborygmus and general abdominal discomfort and bowel disturbances.(3).

Lyon (47) feels that disease of the gallbladder or some part of the biliary system is more responsible for the occurrence of various symptoms of indigestion than any other intra-abdominal organ or disease not excluding appendicitis, peptic ulcer, colitis or intrapabdominal tumor. It may be that as the concept of biliary dyssynergia comes to be more widely recognized and better understood it will come to be thought of as one of the more important forms of biliary tract disease. It may be that such a concept would explain some of the so-called acute gastric upsets in children for which an etiological explanation is often lacking and which usually clear spontaneously.

Ivy (38) states that 1/3 of the cholecystectomy cases have residua. The question is whether they are due to incompetent sphincter, competent sphincter with dilated ducts, hypertonic or hypertrophic sphincter prior to cholecystectomy. He feels that the latter is an important group.

Bisgard and Dornberger (10) in a comprehensive study have shown that gallbladder disease is not confined to middle or later age groups. In a series of 836 cases they found that 18% were under 30 years of age and over 2% were under 20 years of age. Also 40% of the cases in

which the gallbladder was shown to be normal at operation had complained of biliary colic. Cholecystectomy failed to relieve the symptoms in many of the cases which did not have stones and many of the cases which did not complain of colic. Although they drew no such conclusions from this study, it is possible that many cases of functional biliary tract disease were present in this series and led to some of the irregular findings noted above.

Dilatation of the bile ducts and the intrahepatic biliary radicals indicates obstruction to the free flow of bile from the liver into the duodenum caused by calculi, inflammatory reactions, strictures, neoplasms, kinks and functional derangement of the choledocho-duodenal sphincteric mechanism. In the past stress has been laid on the organic factors of common duct obstruction and little attention has been paid to the fact that physiological dysfunction is capable of producing enormous dilatation. But at the present time dyssynergia is the most logical explanation for those cases of hepatic congestion, bile stasis, duct dilatation, jaundice and abdominal distress which at operation offer no pathological explanation. (Best and Hicken, 5).

Biliary dyssynergia will replace many diagnoses of dysfunction due to kinking of the cystic duct, adhesions, scarring, etc. Ten to twenty percent of gallbladder cases may be due to dyssynergia. (Ivy, 38). It is now quite generally conceded that an entire clinical syndrome with symptomatology of biliary tract disease may be caused by a neuro-vegetative dystonia or a pre-

ponderance of either the parasympathetic or sympathetic nervous systems (45,37).

ETIOLOGY

Newman (55) puts forth the following objections to the theory of dyssynergia on the basis of a valve-like action due to the turning on itself of the gallbladder neck. There is no adequate explanation for the hypertrophy of the fundus muscle. Digital compression of the gallbladder fills and distends the neck of the gallbladder abolishing rather than accentuating the"flap-valve" action. Removal of the gallbladder and the cystic duct doesn't relieve the symptoms in all the cases. He states that the same objections apply to the theory of adhesions. Schmieden (46), Ivy (37) and Lipschutz (45) have suggested that might be due to a spastic mechanism which prevented the free flow of bile from the gallbladder into the cystic duct.

The theory of dysfunction due to thickened bile doesn't stand up because the bile from such cases is not thick as a rule. In fact the order of events is the other way round; the bile, if thick, becomes so from remaining in the gallbladder too long. Other factors such as corsets, sedentary life, and diminished abdominal movements, constipation and ptosis have been ruled out.(55).

Newman (55) states that we must not look for a single cause of dyskinesia but for the factors or conditions determining the disorder.

That there is a relation between habitus and gall-

bladder evacuation is still disputed (36) but the feeling is growing that there is a relation between types of dyssynergia and habitus (Newman,55, Lyon,47, Lipschutz,45). Newman states that it occurs in younger individuals and also occurs in characteristic constitutional types as described later (55).

Ivy (37) feels that besides a hypertonic sphincter stasis in the gallbladder may be due to inadequate fat, fruit juices and meat in the diet, stricture of the common duct, ampulla or other pathology, inflammation of the ampulla, duodenitis and duodenal stasis, disturbances of the cystic duct, and, remotely, disturbances of the alleged sphincter at the neck of the gallbladder. Newman (55) believes that dietary factors are particularly important in older individuals. He states that these consist of irregular and hurried meals, possible over appetizing food which results in over stimulation of the biliary tract just as it may result in over stimulation of the gastric part of the gut. He also states that uninteresting, sodden food, mixtures of fats and starches with either very hot or very cold drinks at meal time lead to atony of the stomach, biliary tract and colon. Meltzer (49) suggested that emotional factors or dietary indiscretions might lead to biliary stasis or emotional jaundice.

Psychic factors such as perception of food or fear, anxiety, anxiety and pain have been observed to cause gallbladder contractions with evacuation in both animals and humans (Elman and McMaster,26, Ivy,36). Since such a phenomenon must depend on a nervous reflex, it is ap-

parent that a nervous control of the gallbladder must function and it is not impossible that psychic or emotional factors might alter the function of the extrahepatic biliary tract for better or for worse.

Sussman (71) has shown that the normal gallbladder in the fasting individual or in the one on a carbohydrate diet may go for five days or longer without evacuating.

Lipschutz (45) states that biliary dyssynergia is generally associated with simultaneous spasm in other organs, irritable duodenum, pylorospasm, irritable colon, evidence of food allergy, hay fever and vasomotor rhinitis.

Best and Hicken (5) suggested that inflammation of the duodenum or ampulla might increase the sensitivity of the sphincter but there experience has been that a common duct sphincter may function normally in the presence of a general inflammation of the biliary tract associated with stones, stricture and even pancreatitis.

Experimental evidence indicates that duodenitis or duodenal ileus interferes with the flow of bile into the duodenum. Also clinical and postmortem evidence points to duodenitis as the cause of one type of catarrhal jaundice. (55,38). Giordano and Mann (31) found hypertrophied sphincter of the ampulla in cases of peptic ulcer and attributed these changes to a spasm of the sphincter. Mechanical distention of the stomach has been observed to cause gallbladder contractions (36,15).

It has been demonstrated experimentally in dogs by Shapiro and Kasaback (67) that chronic duodenal obstruction results in definite delay in the emptying time of

the gallbladder. After subsidence of the ileus the delay in emptying persisted in some dogs while the motility returned to normal in others. They suggested that impairment of duodenal motility may result in a greater incidence of infection of the biliary tract. Crain and Walsh (22) demonstrated a definite delay in gallbladder emptying accompanied by an increase in duodenal tonus following the experimental production of a chemical duodenitis. They postulated a disturbance in hormonal production might have occasioned the delayed evacuation. Lipschutz (45) states that a reflex spasm may be produced in choledocho-duodenal mechanism by virtue of an inflammation of the ducts, the passage of a foreign body or the presence of a foreign body in the gallbladder. He states that this brings up the question of which is present first, inflammation, stasis, gallstone formation with subsequent spastic phenomenon or does the sphincterismus precede the others?

Birch and Boyden (9) demonstrated by animal experimentation that faradic stimulation of different parts of the intestinal tract of which the cecum was most sensitive could result in inhibition or excitation of gallbladder evacuation. This led them to suggest that dysfunction and stasis of the gallbladder (with consequent formation of stones might be due in part to inhibitory reflexes arising from chronically diseased portions of the gastro-intestinal tract. But Boyden and Rigler (17) in later work on humans were not able to demonstrate any reflex effect on the gallbladder resulting from stimulation of the gastro-intestinal tract. They believed

this strongly indicated that the human gallbladder is not subject to nerve impulses of extrinsic origin but that it responds only to local pressure changes in its own cavity and to incitatory hormones reaching it through the blood stream. Ivy (37) and Lipschutz (45) both have suggested that constipation might result in reflex interference with gallbladder evacuation. Bartle (3) states that affections of the head may effect the peristalsis and tonus of the gastro-intestinal tract since the afferent impulses from the head come in over the fifth nerve the nucleus of which lies in close apposition to the nucleus of the tenth nerve (vagus).

Ivy (37) submits the following theoretical outline pertinent to the etiology of a hypotonic gallbladder.

Hypotonic gallbladder may be--

a. Primary--congenital muscular deficiency or hypoirritable gallbladder.

b. Secondary--

1. Increased sympathetic or splanchnic activity or reflex inhibition. Constipation? Pregnancy?
2. Hormonal disturbances. Cholecystokinin may not be normally formed. Certain hormones may be produced in excess during pregnancy.
3. Relaxation or paresis secondary to a spastic sphincter. If a spastic sphincter is present for a long time it may lead to relaxation, stretching or paresis of the gallbladder analagous to that which occurs in the stomach.

He also includes in this outline an incompetent or atonic

sphincter.

Atonic or incompetent sphincter--gallbladder would not fill and visualize well. A continous flow of bile into the duodenum would obtain. There would be little or no increase in pigment in the bile after magnesium sulfate, oil or egg yolk. Causes--

A. Primary--congenital, rare.

B. Secondary to--

1. Nervous inhibition of the sphincter.
2. Surgical cholecystectomy.
3. Pathological cholecystectomy due to disease.
4. Atonic duodenum (remotely).

He also submits the following theoretical outline pertinent to the etiology of hypertonic dyskinesia.

Hypertonic dykinesia--a high sphincter resistance with normal or forceful (hyperkinetic) contractions of the gallbladder in response to fats, acid gastric juices or fruit juice producing biliary tract distress, reflex pylorospasm, nausea and vomiting. Due to--

A. Primary--constitutional.

B. Secondary--thought to be due to--

1. Reflex through the vagi.
2. Hormonal imbalance.
3. Irritable duodenum or irritated duodenum.
4. Inflammation of the ampulla.
5. Hypertrophied sphincter.

DIAGNOSIS

In general it may be said that there are two general types of biliary tract disorders of motility. Vagus overactivity results in an overrapid emptying of the gallbladder or spasm of the ampulla with a cessation of bile flow. Vagus undersensitivity (predominant sympathetic control) results in a relaxation of the gallbladder and ampulla and a spasm of the sphincter of Oddi with a cessation of flow. (55). Newman (55) believes he sees more cases of hypertonia but Lyon (4) believes he sees more cases of atonia.

Lipschutz (45) states that history is of little value in differentiating functional from organic disease of the biliary tract except in cases with a definite history of jaundice. But as Ivy (36,37) points out it is possible that jaundice may occur in humans on the basis of dyskinesia alone. Lipschutz goes on to say that if a neurovegetative unbalance can be elicited from the history it is an aid in diagnosis. Dyskinesia is usually found in young adults but atonid dyskinesia is also found in olde r people.

Newman (55) and others feel that duodenal intubation has many great advantages and compares favorably with roentgenographic diagnosis of biliary tract disease. The manner of expulsion may be learned. The effect of drugs on the process may be noted. Bile may be obtained for analysis. Contrary to opinion a negative result is not meaningless. It has the disadvantages that it is more or less unpleasant to the patient and the technical difficulties are somewhat formidable.(55). Intraduodenal in-

tubation is valuable in corroborating a diagnosis of biliary dyskinesia. It is particularly valuable in judging the therapeutic progress of the case. The absence of abnormal microscopic findings in the bile is also an aid in the differential diagnosis. (45). There is a definite relation between a dysfunction of the gallbladder and duodenal drainage (28).

Newman (55) believes cholecystography is of the greatest value but it has the following disadvantages. It tells little about the concentrating ability, it allowes no possibility of chemical study and it tells only roughly how the gallbladder empties. Lipschutz (45) also believes that cholecystography is the most important single procedure in the diagnosis of this condition. Hicken, Best and Hunt (33) feel that only by direct visualization can one obtain evidence of a functional stasis.

The interpretation of cholecystographic findings in regard to the time of evacuation of the gallbladder has changed considerably in recent years. It is possible that this change in thought may result in our picking up more gallbladder disease of a functional type. In the past the observers concerned themselves more with the time necessary for complete evacuation and did not begin their observation until one hour after a fat meal. The habit of making the first observation 1 to 2 hours after the ingestion of a fat meal deprives the clinician of the opportunity of making a diagnosis of dyssynergia. Newman (55) now suggests that many normal gallbaldders may never completely evacuate and more and more author-

ities are suggesting the importance of studying the gallbladder from 15 to 45 minutes after the fat meal to determine the type of response at that time. The gallbladder should begin to empty in ten to twenty minutes following a fat meal; it should be one-half empty in thirty-five minutes; and in ninetyminutes it should be 1/20 of its original size. Not only the time of emptying but the type of emptying should be noted (Newman,55). It is probably true that normally the gallbladder evacuates from 2/3 to 3/4 of its contents within the first 30 minutes after a fat meal and 95% of its contents in about 90 minutes (36). Following the fat meal the gallbladder contractions begin within 5 to 15 minutes with an initial maximum contraction in about 30 minutes. The normal viscus usually shows a marked reduction in volume to from 1/2 to 1/3 of its original size in 30 minutes. (12,28,45,71). In abnormal states the degree of contraction is decreased or even absent. If the gallbladder doesn't contract or empty sufficiently in the 1/2 hour examination the one hour observation rarely reveals any further changes or gives any valuable additional information. (28,45,71). Sussman (71) states that if emptying time is delayed a second fat meal should be given and pylorospasm or obstruction must be excluded.

It is possible that the types of emptying of the gallbladder described under physiology represent kinetic types of function. Type I with a temporary delay of gallbladder evacuation due to an initial relaxation of the gallbladder and simultaneous closure of the

sphincter may correspond to the spastic distension type of dyskinesia and the initial relaxation of the gallbladder may be apparent only. Type II in which a stimulus is followed by a simultaneous contraction of the gallbladder and relaxation of the sphincter might be regarded as the physiologically normal type. Type III in which the time of evacuation is prolonged due to a relaxation of the gallbladder and closure of the sphincter might be regarded as picturing the atonic distention type of dyskinesia.

Spastic Distention

The principle complaint is pain which is described as being dull, grinding, occurring in colicky spasms and lasting several minutes but it is not so severe as colic. There is a constant feeling of soreness. Pain in the right hypochondrium spreads across the abdomen below the rib margins becoming as sever on the left as on the right. It tends to spread to the back to the angle of the scapula. It is often related to exposure or cold or comes on 1 to 2 hours after a meal. Sometines it is temporarily relieved by food. It may simulate duodenal ulcer by night pain and the intermittent periods of attack. Instead of pain, there may be a feeling of distention or fullness after meals. Nausea is common with occasional vomiting which is followed by relief. The vomitus contains acid food. The appetite is poor and the patients lose weight. They may either appear well or quite ill. There is often a history of slight jaundice. The bowels are open more than once a day and the colon is palpable, hard and tender. The

tongue is clean or pale and flabby but is not coated. The liver region is tender especailly over the gall-bladder area, but there is no rigidity or catch as the gallbladder comes down. The liver feels normal. The liver is sore on pressure behind, and the skin is hyper-esthetic. Cardiac irregularities may be due to vagus reflex. (Newman,55).

It is more frequent in the female. It occurs about 36 years of age. Lipschutz (45) also found it occurred more frequently in a younger age level. It is found in persons with a heavy build, having a wide costal angle and broad shoulders but they are not fat. Or it is found in persons with costal angles of about 90 degrees with narrow shoulders but powerful forearms and more than a tendency to axillary sweating. All are active physically and mentally and are given to exertion and athletic sports. Some describe themselves as over strung. (55). A"physiologic block" with a lack of bile flow in the face of an absence of organic cause during duodenal drainage (69). It occurs more frequently in excitable and apprehensive Latin Americans or psychically hyperplastic Jews.

Duodenal Intubation--

Duodenal intubation is usually easy. The gastric juice contains a high normal or an excess of acid. The manometer shows powerful and frequent peristaltic waves. The duodenal juice contains little or no bilirubin. Oil excites a flow of bile only after a prolonged latent period of 15 to 30 minutes. (Newman,55). Lipschutz (45) believes a persistent absence of "B" bile on two or

three drainages is indicative of a ductal or sphincteric spasm while an increase in "B" bile to two or three times the normal volume points to a dyskinesia of the hyperkinetic type. The "B" bile is 40 to 90% bilirubin. Pilocarpine results in an initial cessation of the flow of bile up to five minutes and then a great increase in the rate as the general symptoms wear off. An over filling of the extrahepatic biliary system occurs because of a defective emptying mechanism, the expression of bile being prevented by spasm of the vagus innervated ampullary muscle. The gastric, colonic and cardiac signs could also be due to vagus over activity. It is possible that the introduction of a duodenal tube may provide sufficient irritation to produce spasm in a susceptible sphincter(47). (Newman,55).

Cholecystography

Cholecystography shows an opaque, well filled, well concentrating gallbladder (37) of at least normal size which diminishes after a fat meal but doesn't disappear and emptying is delayed (55). The hypertonic gallbladder empties slowly in phases, shows a dye retention of over 50% at the 1/2 hour examination (45,37). Hypermotile dyskinesia shows complete or nearly complete emptying 30 minutes after a fat meal (28,45,37). The biliary ducts, including the hepatic ducts, can be visualized (37,45). Newman (55) states that the biliary ducts are rarely dilated. The gallbladder is elongated and narrow (45). The gallbladder should empty well and the distress, when present, be relieved by magnesium sulfate, atropine, nitroglycerine or amylnitrite unless edema or

inflammation of the ampulla are present or there is an organic obstruction (37). The stomach is small, horn shaped and of the tonic variety which empties rapidly or if delayed emptying is present it is due to pylorospasm and not to atony (55).

Atonic Distention

In general the patients are older, have slim builds, narrow costal angles, sloping shoulders and poor muscular developement (45,55).

The pain is continuous not spasmodic or colicky but consists of a dull, heavy aching sensation or sense of fullness. It comes on soon after meals, radiates over the entire epigastrium, but not the the back. The gallbladder region is the point of maximum intensity. The appetite is poor and the patient is constipated. They always complain of flatulence. They occasionally vomit but there is surprisingly little nausea. There is tenderness in the epigastrium and over the liver. (55,45).

Duodenal Intubation

The stomach contains little acid and often no free hydrochloric acid. The gastric pressure is low without peristaltic waves but with wide respiratory excursions. The duodenal fluid contains escaped bile but oil evokes a flow only after a long pause. The flow is increased by pilocarpine without a latent period. "B" bile contains low normal amounts of bilirubin. (55). An increase in "B" bile to 2 or 3 times the normal amount points to an atonic dyskinesia (45). Slowness of the bile flow or demand for greater initial stimulus is indicative of atony of the gallbladder, obstruction of the cystic duct or is

due to the viscosity of the bile (3).

Cholecystography

The gallbladder is very long, thin, has a poor shadow and empties poorly (55). Residual dye is present two hours after a Boyden meal (37). Lipschutz (45) believes the atonic gallbladder shows a dye retention of over 50% at the 30 minute examination. The viscus is distended. The atonic gallbladder that empties is not associated with spasm of the sphincter of the common or cystic duct and the atonic gallbladder that doesn't empty is associated with spasm of the sphincter. (45). The stomach is atonic and baggy with a delayed emptying time (55).

TREATMENT

Spastic Distention

Diet

Meals should be small, equal and regular and a mixture of fats and starches should be avoided. Restraint should be laid upon coarse irritating foods and over interesting cookery. Meals should be taken at specific times and preferably should be four a day in number. The patient should avoid buttered toast, mashed potatos (with butter), bread and butter (substitute melba toast. To avoid loss of weight, to avoid fat deficiency and to empty the gallbladder during the resting periods an ounce of butter, olive oil or cream may be taken the last thing at night (55). Ivy (37) suggests essentially the same diet and regime. Lipschutz (45) suggests the avoidance of large quantities of fat which may act to over stimulate the gallbladder. The patient should avoid greasy and rich dishes as well as spicy foods and

condiments. A small quantity of fat in the form of butter, cream and the yolk of soft cooked eggs are permissible if no intolerance is shown to them. Food allergy should be eliminated as far as possible. In both spastic and atonic dyskynesias any tendency toward constipation should be corrected as colonic stasis may produce reflex biliary spasm (or atonia). (45). The daily administration of oleic acid and bile salts for the stimulating effect on the biliary apparatus in conjunction with the above treatment has proven to be very effective in the management of the biliary dyskinesias (45,47).

Medication

Ivy (37) recommends sedation, small doses of belladonna and small doses of heavy magnesium oxide after meals. Lyon (47) also suggests that the spastic group calls for sedation and temporarily lessened emptying effort until the relaxation of the ampulla is controlled by vagal inhibition. Both Lyon (47) and Newman (55) recommend tr. of belladonna /60 three times a day after meals and sodium bicarbonate made up with an infusion of rhubarb. Administration of alkalies if hyperacidity is present is recommended since hyperacidity produces hypermotility of the biliary tract (45).

Lyon (47) says if dyssynergia is associated with pylorospasm a capsule containing atropine sulfate /00012 (or better atropine valerianate /001), luminal /008 or barbital /015 and sodium bicarbonate /3 used three times a day before meals is effective.

In 1935 Best and Hicken (5,6) suggested that the use of atropine, magnesium sulfate and fats to tolerance

might be useful in the treatment of biliary colic following cholecystectomy which cholangiographic studies showed to be due to a spastic sphincter. Later (8) they described a non-surgical routine which they have used successfully in managing foreign body obstructions in the common duct following operation. It is based on the principles of decreasing the resistance to open an exit at the lower end of the common duct and increasing the pressure behind the stone. They report that their results have also been good using this method for non-surgical drainage of the gallbladder. The first day glyceryl trinitrate /0006 is administered three times a day. The second day the patient receives atropine sulfate /0006 three times a day and on the third and last day the glyceryl trinitrate is repeated. Each morning the patient receives magnesium sulfate 8/0 and each evening at bedtime the patient receives olive oil or thick cream 30/0. Also four tablets of decholin or procholin are given four times a day to increase the flow of bile. They warn of the dangers of using a chloretic (decholin) in the presence of an absolute obstruction as severe liver damage may be done by the increase in pressure.

It has been demonstrated that the subcutaneous administration of benzedrine sulfate to cats is followed by relaxation of the gallbladder (29). This might prove to be a means of temporarily relieving the colic associated with a spastic sphincter and a spastic gallbladder. Schube et al (65) demonstrated experimentally in humans that benzedrine sulfate does not cause the gallbladder to

empty and it does not inhibit or prevent the emptying of the gallbladder after a fat meal when the fat meal is given 30 minutes after the administration of the drug at which time the other physiological effects are at their height. But there is a very definite delay in emptying if the fat meal is consumed two hours after the administration of the drug at which time the other physiological effects outside of the central stimulation have worn off. In regard to the point of action of the drug one of the possibilities which they mention is that the sympathetico-mimetic action of benzedrine may cause relaxation of the gallbladder due to sympathetic inhibitory action. Smith and Chamberlain (68) studying the effects of benzedrine in the human observed that benzedrine does not affect the peristalsis of the normal stomach but it exerts a stimulating influence on cases of gastric atony and inhibits gastric hypertony. It has a relaxing effect on smooth muscle in general, delays the emptying time of the stomach and delays small intestinal motility. It does not stimulate evacuation of the biliary system. It increases gastric acidity slightly in normal persons. Lipschutz (45) recommends the administration of antispasmodics and suggests the use of benzedrine sulfate /01 before meals in conjunction with sedatives. Nitroglycerine /0006, atropine /001 hypodermically and amyl nitrite relieves the attacks of colic (37).

Goldstein (32) reports that he has had excellent results in relieving spastic conditions including biliary colic by use of perparin hydrochloride. He feels

that it is safe and more effective than any other known antispasmodic. He also used the new drug trasentin with excellent results.

Einhorn (25) reports that atropine relieves the spasm of neurotropic origin while papaverine relieves the spasm of musculotropic origin. He states that dephenylacetyldiethylaminoethanolester-hydrochloride has 20 times the effect of atropine and its effect is equal to that of papaverine in relieving the two types of spasm. Also the normal intestinal motility was re-established after relieving a spasm of the gut due to barium chloride in contrast to papaverine which was followed by complete paralysis. Its toxicity and side effects are practically nil. It is possible that this may prove to be a very valuable drug in relieving spastic dyssynergia without interfering with intestinal motility or causing the unpleasant side effects found with some of the other drugs.

Duodenal Drainage

Lyon (47) recommends biliary drainage by duodenal tube once or twice a week in courses of four to six repeated if necessary two to three times a year helps to keep the cystic duct patent and the gallbladder bile from stasis as well as having a desirable stimulating effect on the liver cells and on the gastro-duodenal mucosa. Duodenal drainage is also recommended by Lipschutz (45).

Mock, Brown and Dolkart (50) make a plea for the cause of medical or conservative treatment in cases of dyssynergia, chronic cholecystitis without stones,

chronic cholecystitis with large soft calculi few in number with rare or no colic. They remark that surgical treatment in the face of liver damage does not always allow the return of liver function which has remarkable regenerative powers if given a chance. I believe this to be particularly true in cases of spastic dyssynergia, for when and if the gallbladder has been removed and the dyssynergia has not been removed the safety valve in the form of a pressure regulatory mechanism has been lost. They have obtained relief from symptoms in a high percentage of cases by use of medical treatment. Their treatment consists of the administration of ketocholanic acids (ketochol) which have a high choloretic and low toxic effect, hourly feedings of milk and cream and antispasmodic therapy essentially the same of that of Lyon (47).

If the gallbladder functions at all, the treatment should be medical. If the pathology is so far advanced that no function is left, surgery is indicated (47). The gallbladder should be regarded as essential as its removal results in anatomical and physiological changes (59,41). Ivy (38) states that an atonic sphincter favors reurgitation and infection and dilated ducts favor stasis and he believes that the treatment should be surgical since surgical treatment is apt to result in these conditions.

Lipschutz (45) notes that surgical procedures have been advocated and carried out in the past few years. These consist of section of the sphincter or dilatation of the common duct. But he feels that the treatment re-

mains essentially a medical problem. Ivy (37,39) states that cholecystectomy benefits 50 to 75% of the patients having dyskinesia and suggests that the benefit is due to paresis of the sphincter following cholecystectomy. He feels recurrences may be due to recovery of the sphincter tone. Puestow (60) found that a dilatation of the choledochus and permanent loss of function of the sphincter of Oddi occurs after cholecystectomy. He believes that this accounts for much of the relief of symptoms. He feels that most postcholecystectomy pain is due to organic and not functional factors. This is hardly borne out by the work cited elsewhere although to a certain extent he is probably right.

It is probably not entirely true that if the accumulation and stagnation of bile within the ductal system is due to the obstructive action of a hypertonic choledochal sphincter the removal of the gallbladder or surgical drainage of the ducts will correct the sphincterismus or ameliorate the distress.

Atonic Distention

Diet

Fruit and salads should be encouraged. Green and root vegetables should be avoided as well as cheese, porridge, milk puddings and all sodden, doughy, fried and greasy foods. Meals should be taken dry. Food should be tasty and appetizing. In other respects the management would be the same as for spastic distention even as to the nocturnal fat. (Newman,55).

Ivy (37) states that fats, fruit juices and meats

to the tolerance to excite the gallbladder should be taken. The tolerance of each case is an individual problem and may be said to be the amount of cholagogue substances just below the amount that causes symptoms. Lyon (47) advises essentially the same things and states that proteins, starches, carbohydrates and vitamins should be maintained at a normal level. He adds that the best fats are the simple ones,butter,olive oil, cream, bacon, ice cream, yolk of soft boiled eggs, etc. He also advises three to four meals every day regularly spaced and regulary timed; two teaspoonfulls of olive oil with two to three buttered crackers at bed time may substitute as the fourth meal.

Medication

We are handicapped in the use of drugs in that we do not have recourse to specific drugs to combat the disease as in the hypertonic form. We have no drugs which will at the same time depress the sympathetic and stimulate the vagus nerves. (47,55).

Therefore, we are forced to use drugs which increase the gastro-intestinal motility. Newman (55) recommends the following, spirit. armoraciae co.5/0, common horse radish, ol. menthae piperatae /03 to /06, menthol pills /06 and acid after meals. He states that the use of vinegar, pickles and acid drinks in the diet might be of some value.

Lipschutz (45) states that in some cases of atonic dyskinesia associated with hypoacidity, hydrochloric acid should be administered with meals. Here again he recommends the correction of constipation and the ad-

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ministration of oleic acid and bile salts. Lyon (47) suggests the administration of oleic acid in gelatin capsules 1 hour before or 3 hours after meals to assist in emptying the gallbladder. He also recommends the administration of /06 to /18 a.a. of sodium oleate, sodium glycholate and sodium salicylate and /06 of peppermint oil in soft mass pill after meals with the addition of phenolphthalein /02 if laxative is needed.

Duodenal Intubation

Feldman, Maurice and Morrison (28) describe a type of gallbladder which yields excess amounts of thick mucus on duodenal intubation. They suggest that the term "mucus cholecystitis" be applied to this condition. It probably corresponds to the atonic dyssynergia type of gallbladder. They state that duodenal drainage is the treatment of choice although surgery may sometimes be indicated. They report that complete relief from symptoms was obtained by 18 out of 21 patients following treatment with duodenal drainage. Lyon(47) also recommends duodenal drainage and Ivy (37) states that magnesium sulfate by duodenal tube is of benefit.

Flexner, et al (29) have shown that the subcutaneous administration of mecholyl to cats is followed by contraction of the gallbladder. This may prove to be a valuable drug in the treatment of atonic dyssynergia in selected cases.

When cholecystokinin is available for therapeutic administration, it will be a valuable adjunct to medical therapy (47).

THE RELATION OF BILIARY DYSSYNERGIA TO OTHER ORGANS AND DISEASES

Newman (55) suggests a relation between migraine and dyssynergia. He states that migraine has been attributed to biliousness in general and to dyssynergia in particular. He found a rise in blood bilirubin and blood cholesterol content in one case of migraine associated with dyssynergia. He states that relief has been obtained in some cases by non-surgical drainage of the extrahepatic biliary passages. He does not feel that dyssynergia is the cause of migraine because it is continuous and the latter is intermittent. He then wonders whether dyssynergia leads to intermittent liver function failure or whether abnormalities of the liver and the biliary system are two results of a common cause.

Biliary tract disease including colic and jaundice, hepatic neuralgia, normally concentrating but non-evacuating gallbladder and postcholecystectomy pain may be due to biliary dyssynergia (5,39,55).

Newman (55) states that dryness of the throat, and pharynx, dry cough, dysphagia, etc. in the mornings and after meals with neurasthenic symptoms have been reported in association with various liver and gallbladder diseases including dyssynergia. He also states that asthma is said to be associated with spasm of the ampulla.

Confusion has existed in the diagnosis of coronary heart disease and biliary tract disease which has led to mistaken diagnosis and to improper therapeutic measures (47,55). The overactive people who are liable

to spastic distention are also liable to high blood pressure and the two diseases may exist at the same time. Pain should be definitely classified as to site, nature and duration. Does the pain come on suddenly with exertion as in angina or gradually after exertion as in biliary dyssynergia? Residual tenderness lasts for hours after angina but it lasts for days after an attack of gallbladder disease. Gallbladder disease may result in the production of cardiac disease or disorders. Extrasystoles and arrythmias are present in some of those patients with spastic distention. Experimentally in frogs sudden alterations in gallbladder pressure have resulted in asystole, sinus bradycardia and electrocardiographic changes which atropine and section of the vagus have abolished. Newman also states that cholecystitis has been reported as being the cause of auricular fibrillation. He feels that there is no question that the heart can be influenced by the gallbladder. (55)

The stomach both affects and is affected by the biliary system. The hypochlorhydria of cholelithiasis and cholecystitis is well known but whether the function of the stomach is deranged by the biliary disease or whether thetwo go together in the constitutional pattern is unknown. Gastric and duodenal ulcers may cause a reflex overactivity of the biliary mechanism just as over motility in the rest of the gastro-intestinal tract. The same is true of appendicitis and other diseases. Biliary dyssynergia is not likely to be diagnosed and treatment depends on the treatment of the primary cause. (55).

Ivy (36) states that it has been reported that an-

acidity may occur after cholecystectomy but it is not common and it is questionable if it was not present before. There is a tendency in man to anacidity in biliary tract disease not specific in character and not of appreciable significance in the diagnosis or the symptomatology of the disease. It is possible that they are two results of a common cause rather than cause and effect. Experimentally, results have been obtained in both directions so the findings are not significant. He states that the pain, vomiting and respiratory disturbances may result from distention of the gallbladder. Pain is abolished by section of the splanchnics, chiefly the right; nausea and vomiting are abolished by section of the vagi; respiratory disturbances are abolished by section of either vagi or splanchnics; and section of both vagi and splanchnics abolish all responses. Distention of the gallbladder or the biliary passages may induce pylorospasm but after resection of the pyloric antrum in dogs, pain due to biliary tract distention persisted indicating that pain was not entirely due to pylorospasm. Some authorities have thought that the chief symptoms of biliary tract disease are due to motor disturbances of the outlet of the stomach with frequent duodenal spasm and reversed peristalsis. It has been reported that gastric lavage is as effective in relieving biliary colic as morphine. After resection of the pyloric antrum in dogs, pain, nausea and vomiting persisted but to a lesser degree. Again it is possible that we have an association of effects rather than a causal and effect relationship. (Ivy,36).

Newman (55) points out that ligature of the cystic

duct experimentally almost invariably leads to cholecystitis while ligature of the common duct does not as a rule. Also, neuromuscular dyssynergia is dependent on an abnormality of the ampulla of Vater or the sphincter of Oddi which is similar to obstruction of the common duct. But he does feel that some cases of cholecystitis have been contributed to, possibly even essentially contributed to, by "standstill" (absolute block of the cystic duct). Clinically some cases of cholecystitis suffer from the same symptoms after cholecystectomy as they did before. This brings up the question of whether the symptoms were primarily dyskinetic in origin and the cholecystitis was secondarily imposed or whether the dyskinesia was a result of the cholecystitis. If the latter were the case one would expect the nerve reflex disorder to clear when the pathological organ was removed but the symptoms sometimes persist. He makes an analogy between the fact that appendicitis may start as an infection deep in the crypts and the fact that a similar infectious process starting in the crypts of Luschka deep in the muscularis of the gallbladder may set up a subserous inflammation so common in cholecystitis. He also points out that the crypts of Luschka are certainly deepened as the result of dyssynergia. He feels that cholecystis may lead to hypertrophy of the ampullary muscle as does Ivy (37). (55).

Giordano and Mann (31) observed hypertrophic changes in the sphincter associated with cholecystitis and attributed these to spasm of the sphincter. They suggested

that some cases of jaundice and pancreatitis might be explained on the basis of this spasm. Archibald (1) was successful in experimentally producing pancreatitis following the production of a spastic sphincter. Others have suggested that a spastic sphincter might result in stasis, inflammation and gallstone formation (5,39,45,49).

Lyon (47) states that cholecystitis and peptic ulcer occur very frequently in the same patient. Is it possible that the sequence might have been peptic ulcer, dyssynergia, stasis, changes in gallbladder wall and then cholecystitis? An atonic sphincter may allowe the possibility of an ascending infection into the biliary tract (38). Best and Hicken (6) suggest that spasm may result in stasis, precipitation and infection and may be an etiological factor in gallbladder, liver and pancreatic disease. Judd and Mann (41) noted one case in which section of the sphincter allowed the ascent of ascaris into the common bile duct and intrahepatic ramifications.

Westphal (77) found evidence that under vagal stimulation the gallbladder may be not only dyskinetic but it also differs from the normal in its absorptive power. He thought cholesterol is absorbed from the bile by the gallbladder wall there to appear as an ester infiltration. Illingworth (35) describes a case of cholesterosis which had an attack of sever pain in the right hypochondrium radiating to the scapula, jaundice, no fever and the attack was followed by aching pain, sore skin, flatulence and abdominal distention. Pathological examination of the gallbladder revealed no stones, no inflammation, in fact, no pathology outside of cholesterosis. In four

cases in his series the gallbladder showed very little pathological change. He also pointed out that cholesterosis of the gallbladder occurs in a younger age group--about 35 years of age. Inview of the above we may say that cholesterosis of the gallbladder may in some cases be due entirely or in part to dyssynergia slthough it is probably more often the result of other well known processes.

Newman (55) concludes that biliary stasis as a result of biliary dyssynergia cannot be considered as a major factor in gallstone formation and as a secondary factor must be relegated to a very minor place. He does state that what he chooses to term "standstill" on the basis of biliary dyssynergia remains a condition for the spontaneous change of cholebilirubin to hemobilirubin (biliverdin) and its precipitation and therefore may be a contributing factor in the etiology of those pigment-calcium stones not due to the abnormal secretion of bilirubin by the liver. He points out two important reasons against the consideration of biliary dyssynergia as a cause of gallstones. First, stone formation is generally associated with obstruction of the cystic duct and not with obstruction of the common duct and dyssynergia is essentially an obstruction of the common duct. Second, the normal gallbladder probably seldom if ever completely empties itself because of the fact that it is fastened to the liver by a wide flat base, and, therefore, the concept that a residuum left in a gallbladder by incomplete evacuation would be effective in the production of stones is seen to be open to question. The great maj-

ority of individuals probably go through life with some residual bile. (55).

Westphal (77,78) regards biliary dyskinesia as an essential cause of gallstones and produced laminated gallstones in the dog by ligature induced stasis of the distention type (obstruction of the egress of bile from the gallbladder without obstruction to its influx). But Newman (55) feels that these cannot be allowed more than a superficial resemblance to human stones. He states that one group of bilirubin-calcium stone, that found in thin-walled ectatic gallbladders corresponding to atonic distention, are probably due to motility disorder primarily and states that the laminated bilirubin-calcium stones may be due to dyskinesia. He does not recognize dyskinesia as an important factor in the production of other types of stones.

Meltzer (49) and Best and Hicken (5) suggested that a functional disorder of the sphincter mechanism of the common bile duct might lead to stone formation. Ivy (37, 39) states that stasis in the gallbladder results in hyperplasia and hypertrophy of the mucosa and this presumably leads to cholecystitis and stone formation.

Rous and McMaster (63) believe that intermittent biliary stasis is admittedly the principal predisposing cause of stones because of the concentrating activity of the gallbladder which it allowes, resulting in excess bile inspisation. The inspissation of the bile is greatest after a day or two of stasis. Permanent complete obstruction results in white bile formed by replacement of bile by secretion of the ducts. A kind of

agreement is lent to this by Elman and Taussig (27) who point out that cholelithiasis is rarely encountered clinically in patients with malignant obstruction of the common duct but is most common in the hypersthenic type of individual with the rapidly emptying gallbladder. They suggest that if bile by remaining in the gallbladder gains cholesterol and loses bile salts eventual supersaturation and even precipitation of the former might occur. But as is pointed out above (63) this is not what happens, rather white bile is formed by continual obstruction. Also as is pointed out by Ivy (36) and Newman (55) the gallbladder does not secrete any appreciable amount of cholesterol except with inflammation of its mucosa and bile salts are not absorbed to any significant degree by the normal gallbladder mucosa.

As noted under physiology vagus stimulation increases gallbladder resorption (36) and vagus stimulation also causes spastic dyskinesia. Considering the two facts it might be possible that they could predispose toward gallstone formation.

There is no relation between gallbladder evacuation and sex differences except with pregnancy. Reports vary much as to the rate of contraction in pregnancy. Some think the tone of the sphincter of Oddi is increased during pregnancy. (36). Newman (55) feels that a conception of dyskinesia during pregnancy may come to replace the older concept of a hypercholesteremia as being the cause of a higher incidence of gallbladder disease in women. Certain hormones may be produced in excess during pregnancy which interfere with gallbladder contraction and evacuation (37).

Newman (55) states that there is a tendency to substitute biliary dyskinesia for hypercholesteremia as a reason for the preponderance of gallstones in women over men. He states further that the hypercholesteremia of menstruation is a fiction and that of pregnancy is not as common as once supposed. The important thing is that vagal overactivity during pregnancy, if confirmed, would explain some of the attacks of spastic distention and in cases of gallstones this over sensitivity of the vagus provides reason for the rise of symptoms during pregnancy. The pressure of the pregnant uterus has no effect on the biliary apparatus and constipation is associated with dyskinesia because of the common innervation of the biliary tract and colon and not because constipation leads to the formation of scybalae and these press on the bile ducts. Some women have hypercholesterolemia during pregnancy and some of these have excess cholesterol in their bile after delivery and menstrual jaundice has been known for over 60 years. It is said that during every pregnancy and during every period there is excessive excitability of the biliary apparatus leading in many cases to some degree of spastic distention. (55).

Lyon (47) states that pregnancy is accompanied by a doubling in the blood cholesterol and this leads to the formation of cholesterin stones. Whitaker and Emerson (79) believe that pregnancy itself exerts no inhibitory effect upon the emptying of the gallbladder.

It has been demonstrated by Boyden and Gerdes (16) that the curves of evacuation in pregnant women show

marked retardation of emptying when compared with curves from a corresponding group of nulligravida. Examinations 8 to 10 weeks postpartum showed a marked recovery to the normal rate of evacuation but a recovery was not made to a nulligravida mean. They attributed this retardation of flow to a hypertonicity of the sphincter choledochus. This together with a low bile salt-cholesterol ratio and distended gallbladder observed during caesarian section and at postmortem would seem to offer a rational explanation for a greater tendency to calculi formation in the female. They later state (30) that the rate of emptying is essentially normal during the first trimester but is delayed during the second and third trimesters. An alteration in concentrating power of the gallbladder wall also obtains at this time. They suggest that the functional derangement of the sphincter reflects the change in the hormonal content of the organism during pregnancy, and may be due to the action of hormones which inhibit smooth muscle contractions as are found in the uterus and ureters.

The evacuation of the gallbladder in the pregnant dog, guinea pig and gopher is slower and less complete than in the nonpregnant animals (48).

PATHOLOGY

Newman (55) suggests the following possible pathological picture in spastic distention, a hypertrophy of the ampulla muscle, a slight but definite dilatation of the extrahepatic ducts, large strong walled gallbladder, lymphocytic infiltration of the mucosa and a deepening of Luschka's crypts.

He also suggests that in an atonic distention one

might find a long thin-walled gallbladder with a deeply bile stained mucous membrane. The bile ducts are hardly if at all dilated and the muscle of the ampulla is not hypertrophied.

THE EFFECTS OF DRUGS AND AUTOCOIDS ON THE EXTRAHEPATIC BILIARY SYSTEM

KEY--

X.....Stimulates

*.....Inhibits

#.....Causes to Empty

0.....Contradictory

-.....No Effect

R.....Relieves Colic

Drugs	Gallbladder	Sphincter	Empty	Colic
Sympathetic drugs	**	xx	-	
Adrenalin (epinephrine)	** xx - 0	** - 0	- # 0	
Atropine & belladona	** x 0	*** 0	# ?	R
Benzedrine	**		-	
Ephedrine	**	*	# 0	
Parasympathetic drugs	xx	**	#	
Acetyl choline	0	xx 0	0	
Choline	xx 0	0	0 #	
Muscarine	-	xx- - 0	-	
Nicotine	* x 0	** xx 0	#	
Eserine	* 0			
Physostigmine	- 0	xx - 0	0 -	
Pilocarpine	xx	xxx	-	
Papaverine	**	**		
Narcotine	**			
Pantopon	x	x	-	
Cocain	**			
Novacain	** - 0		-	
Ether	**			
Nitrites	**	***	#	R
Calcium ion	**			
Veratine	**			
Magnesium chloride	** x 0		#	
Alcohol	x 0	-	#	
Phenol	**			
Sodium salicylates	** -		-	
Histamine	* xx 0	xx	# - 0	
Magnesium sulphate in duodenum	xx	**	##	R
Magnesium sulphate intraven.	**			
Peptone	xx			
Barium chloride	xx		#	
Calomel	x		-	
Cholecystokinin	xxx	***	###	
Fat meal	xx	**	##	
Hydrochloric in duodenum	xx 0	x 0		
Olive oil	xxx	***	###	R
Butyric acid in duodenum	xxx	***	###	
Lead acetate			#	
Soap	xx	**	#	
Butter	xxx	***	###	
Sodium sulphate	x	*	#	
Pitruitrine	x	*	#	
Ergotamine	xx - 0	-	-	
Morphine	xx 0	xxx	-	
Chloral hydrate	xx			
Potassium ion	xx			
Methyl Guanidine	**			
Ergonovine	**			
Sodium nitrite	**			
Trasentine	**			
Syntropan	**			
Nitroglycerine	**	***	###	R
Quinine	x			
Pitocin	xx			
Pitressin	x			
Cyanide	xx			
Calcium chloride	xx			
Egg yolk	xxx	***	###	
Oleic acid	xxx	***	###	
Cod liver oil	xxx	***	###	

Drugs	Gallbladder	Sphincter	Empty	Colic
Cocoanut oil	xxx	***	##	
Palmitic acid	xx	***	##	
Peanut oil	xx	***	##	
Castor oil	xx	***	##	
Lard	xx	***	##	
Cream & milk	xx	***	##	R
Mecholyl	x			
Amyl nitrite	**	**	?	R
Bile salts (decholin)		**		
Magnesium oxide		**		
Oxytoxin		**		
Acid		** 0		
Scapolamine		**		R
Theophylline & ethylenedianine		**		
Eating		**		
Alkali		xx 0		
Sodium bi-carbonate		xx 0		
Dilaudid	x	x		
Codein	x	x		
Fasting		xx		
Distention in the stomach		xx		
Guanidine	-	-	-	
Benzyl acitate & alcohol	- x 0	-	- 0	
Caffein	-	-	-	
Procain	-	-	-	
Strychnine	-	-	-	
Carbinoyl choline	0	0	0	
Yohimbine	0	0	0	
Sodium tartrate			#	

This chart is include merely because there is such a difference of opinions as to the action of various drugs on the extrahepatic biliary system it is hardly worth while discussing them separately. Some comment is probably in order, however.

1. The greater number of authorities describe a moderate contraction of the gallbladder and a flow of bile after the intraduodenal introduction of dilute hydrochloric acid.

2. Some (15) feel that magnesium sulfate, magnesium chloride, sodium sulfate and sodium tartrate are as effective orally as intraduodenally.

3. Atropine counteracts the effect of pilocarpine, is not effective after morphine and does not prevent effect of cholecystokinin.

4. Atropine acts by paralyzing the vagus, morphine acts directly on the gallbladder and sphincter muscle.

5. Cholecystokinin is not effective after nitroglycerine.

6. Amyl nitrite and nitroglycerine relax the spasm produced by morphine.

7. Barium produces spasm by musculotropic action.

8. Fresh fats are not effective in producing evacuation of the gallbladder. Action depends on their digestion or rancidity.

(1,5,6,7,8,15,19,24,26,29,31,33,36,37,38,39,40,46,49,52,54,74,etc.)

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